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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/671,687	09/28/2000	David Wallach	WALLACH=25	7238

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EXAMINER	
LAMBERTSON, DAVID A	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 11/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/671,687	WALLACH ET AL.	
	Examiner	Art Unit	
	David A. Lambertson	1636	

-- The MAILING DATE of this communication appears on the cover sh t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,20-24 and 38-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,20-24 and 38-43* is/are rejected.

7)☒ Claim(s) *3 and 44-46* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. *09/646,403* .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *1003* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn. As per the contents of the interview summary and Applicant's request for reconsideration, the Examiner has dropped the rejection under 35 U.S.C. § 112, first paragraph concerning Written Description.

Claims 2-4, 20-24 and 38-46 are pending in the instant application, and are ready for examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 20-24 and 38-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated protein capable of binding to TRAF2 and having the amino acid sequence of SEQ ID NO: 3, molecules which bind to this sequence and compositions comprising the protein, does not reasonably provide enablement for variants having 85%, 90% or 95% identity to SEQ ID NO: 3 and having the ability to bind to TRAF2, or fragments of SEQ ID NO: 3 that have the ability to bind to TRAF2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the specification coupled with information known in the art without undue experimentation (*United States v. Telectronics.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is needed is not based upon a single factor but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988), and the most relevant factors are indicated below:

Nature of the invention. The nature of the invention is an isolated protein having the amino acid sequence of SEQ ID NO: 3, a variant having 85%, 90% or 95% identity to SEQ ID NO: 3, and fragments of these amino acid sequences, wherein each sequence or fragment thereof has the ability to bind to the tumor necrosis factor receptor-associated 2 protein (TRAF2). The invention is also directed to compositions comprising the isolated proteins/variants/fragments, as well as molecules that have the binding portion of an antibody having the capacity to bind to the isolated proteins/variants/fragments. Thus in order to make and use the invention, the skilled artisan would be required to make a protein having the ability to bind to TRAF2.

Notably, SEQ ID NO: 3 is 949 amino acids in length. Thus a protein having 85% identity would have up to 142 amino acids changed, while proteins of 90% and 95% would have up to 95 and 48 amino acids changed, respectively. For example, a protein can have 85% homology to SEQ ID NO: 3, where the N-terminal 142 residues are completely different from those of SEQ ID NO: 3; significantly, this 142 residue amino acid sequence can represent a decent sized protein, as well as an independently functioning domain. In other words, a fragment of a protein having 85% identity with SEQ ID NO: 3 can actually be an independent protein.

Even within the context of being covalently linked to the portion of SEQ ID NO: 3 with which it has 85% identity, this 142 amino acid sequence could fold into an independently functional domain (i.e., functions with an activity that is not affected by the remaining protein having identity with SEQ ID NO: 3). Thus, the nature of the invention comprises all sequences having up to 142 amino acids in length that have the ability to bind to TRAF2.

In a different example, a protein can have as high as 95% homology to SEQ ID NO: 3, where the C-terminal 48 residues are completely different from those of SEQ ID NO: 3; significantly, this 48 residue amino acid sequence can represent a functional domain for a protein, a domain which can also fold and function independently of the rest of the protein. Therefore, the nature of the invention also includes protein domains that have not been discovered or made, which may have the ability to bind to TRAF2 either as a protein fragment, or in the context of a larger protein.

Finally, it is important to recognize that meeting the enablement standard requires that the skilled artisan be able to make the invention, and that making the invention and identifying the invention are not synonymous.

Scope of the invention. The scope of the invention is very broad. As indicated in the Nature of the Invention, when interpreted as broadly as possible and in view of the mathematical limitations, Applicant has claimed any protein having up to 142 amino acids that has the capacity to bind to TRAF2. Because the claims indicate fragments of variants (see claim 2(C)), this 142 amino acid sequence does not even require *any* identity to SEQ ID NO: 3. Even in the context of a protein having 95% identity to SEQ ID NO: 3, the claims include a protein that can have an independently functioning domain within the context of a larger protein (essentially a gene

fusion), wherein the product of the gene fusion has the ability to bind to TRAF2. Additionally, the claims include antibodies that recognize fragments of variants having 85% (or 90% or 95%) identity to SEQ ID NO: 3, such as the 142 amino acid sequences which have no identity with SEQ ID NO: 3.

State of the art and Level of skill in the art. The State of the Art concerning SEQ ID NO: 3 is silent. There is no indication in the prior art of the particular sequence, thus it is a novel sequence. However, there is also no indication in the prior art that guides the skilled artisan to be able to make a protein having 85%, 90% or 95% identity to SEQ ID NO: 3, or a fragment thereof, where either the fragment or variant retains the ability to bind TRAF2. This is because there is no disclosure in the prior art indicating the minimum sequence/structural requirements for SEQ ID NO: 3 to bind to TRAF2. In the absence of such teachings, the skilled artisan could not make and use the claimed fragments and variants that retain the activity

The instant application is claiming protein variants or fragments thereof that have the functional ability to bind to TRAF2 based on homology alone. As it regards the general art of predicting function based on homology, the prior art indicates the unpredictability associated with such an endeavor. A particular example involves the identification of a specific protein involved in Pendred Syndrome, PDS. PDS was originally identified by Everett *et al.* (*Nature Genetics* **17**: 411-422, 1997; see entire document; henceforth Everett), who predicted that the PDS gene product encoded a sulphate ion transport protein based simply on its homology to a family of known sulphate ion transporters (see for example the Abstract and page 419, right column, second full paragraph). However, a subsequent study performed by Scott *et al.* (*Nature Genetics* **21**: 440-443, 1999; see entire document; henceforth Scott) indicated that PDS was in

fact not a sulphate ion transporter. In fact, PDS was completely unable to transport sulphate ions across a membrane (see for example the Abstract and page 440, the paragraph bridging the left and right columns). Rather, Scott discovered that PDS was a chloride and iodide ion transporter (see for example page 440, right column, second and third full paragraphs), a finding that Scott indicates as underscoring the importance of confirming the functions of proteins, even in the face of significant homology (see for example page 441, left column, third full paragraph). This is further supported in the article by Berendsen (*Science* **282**:642-643, 1998), which approaches the problem of predicting structure-function relationships based on homology from the perspective of high-performance computing. Berendsen indicates that, while it is desirable to be able to predict structure from function, it is extremely elusive, and is similar to King Arthur's quest for the Holy Grail (see for example page 643, paragraph bridging the left and central columns). Thus, the state of the art clearly indicates that assigning a function to a protein based on homology alone is highly unpredictable.

Number of working examples and Guidance provided by applicant. The instant specification provides the identification of a protein indicated as SEQ ID NO: 3, and describes its ability to bind to TRAF2. However, the characterization of the protein ends there, with no indication of what sequences or domains of SEQ ID NO: 3 are required for this interaction with SEQ ID NO: 3. Armed with only this teaching, the skilled artisan would not be able to make the claimed invention of fragments and variants of SEQ ID NO: 3 that can bind to TRAF2, let alone any protein having up to 142 amino acids with absolutely no identity to SEQ ID NO: 3 that also has the ability to bind to TRAF2.

The instant specification provides teachings that are known in the art that can be used to identify protein sequences that bind to other protein sequences; such teachings include two-hybrid protein interaction systems and co-immunoprecipitation assays. The specification indicates that these teachings can be used to identify fragments, variants, and fragments of variants of SEQ ID NO: 3 that have the ability to bind to TRAF2, and suggests that such experimentation would not be undue. However, as indicated in the Nature of the Invention section of the Wands analysis, the ability to identify is not commensurate with the ability to make and use, which is the standard for meeting the enablement requirement.

Unpredictability of the art and Amount of experimentation required. The invention is highly unpredictable, and requires a good deal of trial and error experimentation in order to make and use the claimed invention. There is nothing in either the prior art or the instant specification to indicate what fragments of SEQ ID NO: 3 are capable of binding to TRAF2 because there is no indication of what sequence or structural requirements of SEQ ID NO: 3 are required for this binding activity. Therefore, the skilled artisan could not predictably make fragments of SEQ ID NO: 3 that bind to TRAF2. Similarly, without the knowledge of the TRAF2 binding domain of SEQ ID NO: 3, the skilled artisan could not predictably make variants of SEQ ID NO: 3 that bound to TRAF2 because the skilled artisan could not predictably make a mutation that does not affect the binding activity of SEQ ID NO: 3. Furthermore, the skilled artisan could not predictably make any protein of 142 amino acids in length having no identity to SEQ ID NO: 3 (which is included by the claim of a fragment of a protein variant having 85% identity to SEQ ID NO: 3) that has the ability to interact with TRAF2 because the skilled artisan could not predict

which 142 amino acid proteins would have a TRAF2 binding domain, there being no teaching as to what such a binding domain would comprise in terms of sequence and structural requirements.

The teachings that there are assays to identify what variants, fragments and fragments of variants of SEQ ID NO: 3 will bind to TRAF2 does not assist in the ability to *make and use* these variants, fragments, and fragments of variants; it is reiterated that the ability to identify does not translate into the ability to make and use. Rather, the fact that an assay is required to identify these proteins represents an indication that unpredictable and undue trial and error experimentation is required to make and use the claimed invention. As it regards the identification of fragments of SEQ ID NO: 3 that bind to TRAF2, the skilled artisan would be required to create a large number of fragments of a 949 amino acid protein, with no ability to predict which portions of the protein are required for the binding activity. In an even more complicated situation concerning fragments of variants of SEQ ID NO: 3, the skilled artisan would have to randomly test 142^{20} (142 amino acids with 20 different possibilities at each position) polypeptides for their ability to bind to TRAF2, with no ability to reasonably to predict which polypeptides could bind to TRAF2; this would continue in a subtractive mode for each length of polypeptide (i.e., the skilled artisan would then have to test 141^{20}, 140^{20}, 139^{20}, etc. polypeptides), again with no reasonable ability to predict which polypeptides have the ability to bind to TRAF2. The conclusion that this would not represent undue and unpredictable trial and error experimentation argues against logic. Rather, the requirement for an assay to identify variants, fragments and fragments of variants of SEQ ID NO: 3 that have the ability to bind to TRAF2 represents an invitation to experimentation in the absence of any significant guidance in

either the prior art or the instant specification concerning the sequence/structural requirements for SEQ ID NO: 3 to bind to TRAF2.

In conclusion, it is urged that the ability to identify a sequence with a function does not equate to the ability to make and use such a sequence, which is the standard for meeting the enablement requirement of 35 USC § 112, first paragraph. The instant claims are very broad, not only including fragments of a protein and variants of a protein having homology to a protein (SEQ ID NO: 3) that has a particular activity, but also including a large number of proteins that have no homology whatsoever to the known protein. Neither the instant specification nor the prior art provides any guidance indicating the sequence and structural requirements for SEQ ID NO: 3 to bind to TRAF2. Significantly, the variants and fragments of SEQ ID NO: 3 having the ability to bind to TRAf2 are claimed based simply on homology to the SEQ ID NO: 3, with the prediction of a functional capacity to bind to TRAf2 based simply on that homology; however, the prior art indicates that predicting function based simply on sequence homology is unpredictable. Thus, in order to make the claimed invention (as opposed to identifying the claimed invention) in the absence of adequate teachings by either the prior art or the instant specification, the skilled artisan would be required to practice undue and experimental trial and error experimentation to test all of the claimed variants for function. Therefore, it is determined that the broad scope of the invention is not fully enabled.

Allowable Subject Matter

No claims are allowable.

Claims 3 and 44-46 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (703) 308-8365. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

David A. Lambertson
AU 1636

JAMES KETTER
PRIMARY EXAMINER